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Off-label use of medicines in neonates, infants, children and adolescents: a joint policy statement by the European Academy of Paediatrics and the European Society for Developmental, Perinatal and Paediatric Pharmacology

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Abstract:	Health care professionals who prescribe medicines have the professional duty to choose medicines that are in the best interest of their individual patient, irrespective if that patient is an adult or a child. However, the availability of medicines with an appropriate label for paediatric use is lagging behind those for adults, and even available paediatric drugs are sometimes not suitable to administer to children. Consequently, health care professionals often have no other option than to prescribe off-label medicines to children. An important reason for use of off-label medicines is to improve access to (innovative) treatments or to address medical needs and preferences of patients, especially when no other options are available. However, off-label use of medicines is in general not supported by the same level of evidence as medicines licensed for paediatric use. This may result in increased uncertainty on efficacy as well as the risk for toxicity and other side effects. In addition, liability may also be of concern, counterbalanced by professional guidelines. Conclusion: The

	purpose of this joint EAP/ESDPPP policy statement is to offer guidance for physicians on when and how to prescribe off-label medicines to children and provide recommendations for future European policy.
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Abstract

Health care professionals who prescribe medicines have the professional duty to choose medicines that are in the best interest of their individual patient, irrespective if that patient is an adult or a child. However, the availability of medicines with an appropriate label for paediatric use is lagging behind those for adults, and even available paediatric drugs are sometimes not suitable to administer to children. Consequently, health care professionals often have no other option than to prescribe off-label medicines to children. An important reason for use of off-label medicines is to improve access to (innovative) treatments or to address medical needs and preferences of patients, especially when no other options are available. However, off-label use of medicines is in general not supported by the same level of evidence as medicines licensed for paediatric use. This may result in increased uncertainty on efficacy as well as the risk for toxicity and other side effects. In addition, liability may also be of concern, counterbalanced by professional guidelines.

Conclusion: The purpose of this joint EAP/ESDPPP policy statement is to offer guidance for physicians on when and how to prescribe off-label medicines to children and to provide recommendations for future European policy.

List of abbreviations

BNF-c: British National Formulary for Children

CJEU: Court of Justice of the European Union

EAP: European Academy of Paediatrics

ESDPPP: European Society for Developmental, Perinatal and Paediatric Pharmacology

GP: general practioner

HCP: health care professional

PICU: paediatric intensive care unit

PTLD: post-transplant lymphoproliferative disease

NICU: neonatal intensive care unit

NKFK: Dutch Expertise Centre for Pharmacotherapy in Children

RTU: recommendations for use

SmPC: summary of product characteristics

Introduction

Health care professionals (HCPs), in close collaboration with pharmacists, who prescribe medicines, have the professional duty to choose medicines that are in the best interest of their individual patient. However, the availability of medicines with an appropriate label for paediatric use is lagging behind those for adults and available paediatric drugs are often not suitable to administer to children [1]. As a result, physicians often have no other option than to prescribe medicines to children outside the approved conditions for age, therapeutic indication, dose recommendation, formulation and/or route of administration (i.e., off-label use [2]) or to prescribe a drug which has not received a license for use in adults or children (i.e., unlicensed medicines use [2]). The practice of off-label prescribing of medicines to children is substantial, both in hospital care and primary health care [3]. A recent report on the setting in the European Union indicates that off-label use of medicines in children is still widespread. Off-label use varies among European countries, with 13-69% of prescriptions being off-label in the hospital setting and 2-100% in primary care [4].

European guidelines on off-label use of medicines in children could greatly benefit children, parents and their HCPs. Therefore, the purpose of this policy statement is to offer guidance for these HCPs, and to provide recommendations for any future European policy.

European views on off-label use of medicines

According to recent survey findings among European stakeholders, off-label use of medicines is perceived to have both advantages and disadvantages. An important advantage is the accelerated access of patients to (innovative) treatments and the appropriate treatment of medical conditions in patients, when no other options are suitable [4].

The development of medicines for children is complicated by a small and heterogeneous market, and methodological and ethical requirements for paediatric trials [5]. As a result, many medicines are not labelled for use in children. It has been estimated that more than 50% of medicines used in children have not been tested for the specific age group [6]. In addition, medicines labelled for use in children may underperform with respect to their ability to provide the recommended dose, the suitability of the dosage form and the presence of potential harmful excipients [7]. For example, the availability of melting or chewable tablets, more likely taken by younger children, appears to be limited [1]. Typical therapeutic areas of off-label use in children include – but are not limited to - infectious diseases, cardiology, dermatology, pain treatment, alimentary tract and metabolism, the respiratory system and the central nervous system [4]. The highest frequency of off-label use of medicines is seen in patients treated in the NICU, PICU and children with oncologic diseases.

By using off-label medicines, prescribers, children and their families have more treatment options to discuss in order to provide a treatment that one finds most appropriate for the needs of the individual patient. In addition, based on the newest available scientific evidence, (innovative) medicines (type of drug, dose and/or indication) can be prescribed to patients at an earlier stage before the required regulatory approval has been finalized, or adapted [4]. However, as off-label use of medicines are in general not supported by the same level of pre-clinical and clinical evidence as medicines licensed for paediatric use, this may result in increased uncertainty on efficacy as well as the risk for toxicity [7] and prescribers and patients have less information at their disposal to decide to choose (prescriber) or accept (patient) the off-label treatment [4]. Finally, the issue of liability may also be a concern, counterbalanced by available professional guidelines [4].

Off-label prescribing is not regulated by European law [9]. European legislation only regulates the marketing of medicines and not the way medicines are ultimately used in clinical practice, which is a national competence, or is captured in 'para'legal statements or guidelines on good practice. Prescribing on-label or off-label medicines is a decision taken within the relationship between a patient and the prescriber. The professional setting (both legal, and 'para'legal) does not limit the right of prescribers to prescribe medicines to "on-label" prescriptions only, as this would in many cases lead to a conflict of professional duties. Therefore, in practice, at the national level off-label use of medicines is often ethically and legally 'accepted' under restrictions.

Several European countries have adopted special statutory regulations for off-label use of medicines, and have good practice or professional guidelines for use, including reimbursement decisions (**Tables 1-3**). These regulations or policy tools aim for improvement of knowledge regarding efficacy and safety of off-label use. This regulation to encourage pharmaceuticals to file a license extension and/or to create the opportunity to apply research results immediately in a licensed setting, are counterbalanced by the uncertainties related to reimbursement practices. In countries where no policy tools are in place, the predominant argument is that off-label use of medicines is an issue that should be dealt with in the context of the relationship between prescriber and patient rather than at level of the regulatory or healthcare system [4].

European policy statement on prescribing off-label or unlicensed drugs to children

Off-label use of medicines is subject to several conditions. According to the Court of Justice of the European Union (CJEU), off-label use should remain exceptional in order to preserve the practical effect of the licensing procedure for medicines. Prescribing off-label medicine: (1) should be limited to individual situations justified by medical considerations; (2) should be under the responsibility of the prescriber; (3) presupposes that the medicine is necessary to address the needs of the patient; (4) should follow a full assessment and examination of the patient, and (5) should be decided on the basis of purely therapeutic considerations [4].

Physicians who prescribe off-label medicines to children should comply with ethical and professional standards. Divergence in drug and social laws, institutional, and professional rules across Europe may complicate a uniform approach to prescribing off-label medicines in children. Nevertheless, the European Academy of Paediatrics and the European Society for Developmental, Perinatal and Paediatric Pharmacology strongly recommend that the following conditions are considered when prescribing off-label medicines to neonates, infants, children or adolescents. We hereby suggest that this may serve as a checklist for defensible, good practice.

Condition #1: All other options, including the use of medicines approved by the regulatory authorities, are unavailable, not tolerated, less than optimal, too expensive, not reimbursable by insurance companies, or containing potentially harmful excipients.

Off-label use is not the same as off-knowledge use.

Condition #2: The prescriber is competent to prescribe off-label medicines in children.

An off-label medicine can only be prescribed by someone who has prescribing skills (rational drug therapy) and is knowledgeable about off-label use of medicines in children [10]. Importantly, in this process there is a major role of the pharmacist who is able to provide or produce the drug extemporaneously. As children differ from adults with regards to disease aetiology, pharmacokinetic and pharmacodynamic factors and formulation acceptance, the prescriber should have specific knowledge and experience in the field of paediatrics. Although most physicians appear to be familiar with the practice of off-label prescribing, most are not aware that the medicines they prescribe are indeed off-label medicines [11]. As this may have consequences for the monitoring of efficacy and adverse events, it is crucial that the prescriber should be aware that he or she is prescribing the medicine in an off-label manner.

Condition #3: Off-label prescription of the medicine is appropriate to meet the needs of the individual patient within the available resources.

There are several situations in which it may be necessary to prescribe a medicine in an off-label manner.

- There may be a medical need where there is no labelled medicine available [4], or the labelled formulation or dosage is not age-appropriate. For example, most medicines used in neonatology have not been tested for the appropriate age and weight group and most doses have been extrapolated from adult and older children. Moreover, the risk of administration errors can be reduced if age-appropriate off-label drug formulations are prescribed. In addition, off-label use is the rule and not the exception in patients with rare diseases, like clobazam for epilepsy in Dravet syndrome.
- Certain medicines may be licensed, available and suitable for use in children in one country, but not in another; for example midazolam oral suspension that is available in Germany but not in Belgium.
- The licensed medicine may (no longer) be appropriate (has become obsolete), for example due to the use of harmful excipients, and an off-label medicine provides an appropriate alternative to use.
- An off-label medicine may address patient needs better than the licensed medicine in cases when the licensed medicine is not effective, or causes unacceptable side effects, resulting in lower treatment adherence [4].
- Off-label use may be part of the professional treatment guideline [4], for example in cases where product summaries have not been updated (yet) despite available evidence [12], such as aminoglycoside dosing in neonates and infants. This type of off-label use allows physicians to use existing medicines in an innovative way, when evidence exists but formal licensing for children has not taken place (yet) [4], as may be the case in paediatric oncology (e.g., rituximab for treatment of post-transplant lymphoproliferative disease (PTLD).

Condition #4: The off-label prescription should be rational and clinically appropriate.

As with licensed use of medicines, the prescriber must ensure the off-label prescription is appropriate [4]. All medicines have associated risks of adverse events. In the case of on-label prescribing, the prescriber can rely on the medicine's evaluation by the competent authorities. In the case of off-label prescribing, the prescriber has to weight the benefit-risk ratio. Off-label prescribing is considered appropriate if (1) it is justified by best available evidence, preferably based on professional guidelines supported by relevant societies (e.g. national paediatric and/or pharmacist societies); (2) it occurs within the context of a formal research protocol; or (3) it pertains to exceptional use, justified by individual clinical circumstances. If none of these justifications is present, its use is generally not recommended [adapted from 13].

If off-label prescribing is considered appropriate, the prescriber will not automatically be liable for negative impacts on the patient's health, especially if the off-label use is mentioned in a professional guideline or formulary.

Rational pharmacotherapy requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own requirements, for an adequate period of time, and at a reasonable cost to them and their community [14]. Formularies may be effective in improving rational pharmacotherapy in children [15]. In the United Kingdom and The Netherlands, physicians prescribing medicines to children are guided by information in the British National Formulary for Children (BNF-c) and the Dutch National Formulary for Children. In the Netherlands, the development of this open-access formulary has resulted in the revision of many consensus-based dose recommendations, and ensured uniformity in prescribing habits in the Netherlands [16]. However, it is important to emphasize that these formularies have still knowledge gaps, like for optimal use of medicines in preterm neonates.

Condition #5: The patient, parents/caregivers should be informed and involved.

When considering prescribing an off-label medicine, both children and their parents/caregivers should have all the appropriate information available, if possible, regarding that medicine.

There is limited published literature about the views of patients, parents and healthcare professionals regarding informed consent in off-label or unlicensed use of medicines in children. In general, most

children [17], parents [11,18], and citizens [19] feel that parents should be informed when a medicine is prescribed in an off-label or unlicensed manner, for example to create alertness to potential side effects [17]. In addition, most children feel that also the child (in case of older child) should be informed [17]. The literature from health care professionals is more mixed: most healthcare professionals in Northern Ireland [20] felt that parents should be informed, whereas hospital-based paediatricians in Scotland did not [21]. Knowledge about off-label or unlicensed use of medicines in children is low among the general public [19] and in different studies of parents of healthy and chronically ill children [11,18]. A minority of hospital-based paediatricians [21] and of general practitioners [22] (GP) in Scotland informed a child's GP [21] or the parents [22]. Once parents knew that their children were prescribed off-label medicines, parents would ask for a licensed medicine [18,19] or they would use the medicine with more caution [19]. The percentage of refusal of off-label use was higher among parents of healthy children compared with parents of chronically ill children [23].

Several national policy tools indicate patients should be informed and provide consent when prescribing off-label or unlicensed medicines (**Tables 1 and 3**). According to the Royal College of Paediatrics and Child Health, in general, when prescribing off-label medicines to children, it is not necessary to take additional steps to obtain consent of parents, caregivers and children beyond those taken when prescribing licensed medicines [24]. This is in line with the policy statement issued by the American Academy of Pediatrics in 2014, which states that administration of off-label medicines in children does not warrant special consent if it is based on sound medical evidence. However, if the off-label use is experimental, then the patient (or parent) should be informed of its experimental status [25]. European paediatricians should know and abide by the appropriate informed consent laws in their respective countries.

Condition #6: The patient should be monitored for efficacy and adverse events.

As off-label or unlicensed use of medicines may result in altered efficacy and an increased risk for harm and hospitalization [8], the prescriber and pharmacist should ensure appropriate monitoring. Adverse events should be reported to the national pharmacovigilance system by HCPs, but also by the families

(parents and or children). In case where medicines are prescribed that have reasonable rationale for use, but insufficient evidence to mitigate safety, efficacy and cost-effectiveness concerns, yet they are not part of clinical research ("innovate off-label use"), then outcomes should be evaluated prospectively, documented appropriately, and reported to all stakeholders (health care providers and patients) in a timely fashion. Regular review should occur to reduce the risk of continued use that is not efficacious or is unsafe [28]. In this way, this condition is true for any prescription, including off label or unlicensed use.

Condition #7: The prescriber should consider if off-label prescribing should be part of a clinical trial.

Finally, in order to increase our knowledge about the efficacy and safety of all medicines used in children, the prescribers should be informed about clinical trials involving off-label medication in which the patient could participate and inform the parents and – when applicable – also the children.

Policy Statement: recommendations

Off-label and unlicensed prescription practices occur. In order to facilitate the clinical practice of appropriate, rational and safe prescribing of off-label medicines to individual children, the EAP and ESDPPP strongly recommend that

- All physicians prescribing medicines to neonates, children or adolescents have access to reliable and up-to-date information (where possible) on the medicine they prescribe. A European paediatric formulary with the best evidence on dosing and safety information could be a useful tool for improving the rational use of medicines in children and adolescents [15]. The BNF-c and the Dutch Formulary could serve as templates [16].

- Paediatric clinical pharmacologists/paediatricians/paediatric pharmacists should be actively involved/consulted in decision-making processes by hospital, Pharmacotherapeutics Committees and national health care authorities.

- Enhanced safety monitoring and reporting by parents and caregivers should be promoted when off-label medicines are prescribed.

- Parents and patients but also the public should be educated about off-label and unlicensed use of medicines.

- Where off-label use of a medicine is common and evidence-based, it should be the shared responsibility of marketing authorization holder and the relevant regulatory authorities to take appropriate measures to address legal uncertainty and safety concerns.

- Health authorities and health insurances should support, and thus reimburse, therapeutic practices that are evidence-based or advocated by a respectable and responsible body of professional opinion, regardless of labelling status.

- Legislation should be adopted that aims to effectively stimulate research into off-label medicines, including non-publication of clinical trial data [29]) and facilitate the registration of off-label uses with a positive benefit-harm balance.

Conclusion

HCPs often have no other option than to prescribe medicines to children outside the approved conditions for age, therapeutic indication, dose recommendation, formulation and/or route of administration. This EAP/ESDPPP policy statement is intended to offer practical guidance to these HCPs on when and how to prescribe off-label medicines to children. Several conditions should be considered when prescribing off-label medicines. This list of conditions may serve as a checklist for defensible, good practice.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval and informed consent

This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, ethical approval or informed consent do not apply.

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Table

Table 1: National temporary recommendations for off-label use of medicines[a]

Country	When off-label prescribing?	How?
Belgium	The evaluation of the individual practitioner's choice implies an evaluation of possible alternatives, including alternative treatments, alternative medicinal treatments, and alternatives to a treatment, but in essence there is 'therapeutic freedom'.	After informed consent of the parents and patient, and after clinical examination.
France No. 2011-2012 act (RTU)	If prescriber deems it necessary for patient, given scientific knowledge and absence of available alternative treatment Or If medicine is part of "Recommendations for use (RTU)" scheme. An RTU for off-label use can be issued by the French Agency if certain criteria are met.	Prescriber must justify choice; Informed consent is required; If medication is part of RTU: prescriber should mention this on prescription, so that pharmacists can control prescription in this context. The marketing authorisation holder should set up patient follow up. RTU medicines are reimbursed by the national health insurance.
Italy National Law n. 94/98 (Di Bella Law), 648/96 national Law	If indication relates to therapeutic area with unmet medical need and Companies do not want to perform clinical trials for given indication.	Off-label use requires support of phase II completed study; Informed consent is required; Reimbursed if application of law 648/96
Spain National Royal Decree No. 1015/2009	Off-label use has to be exceptional and only limited to those situations in which no approved alternative exists, with respect to any restriction of the conditions for prescribing and dispensing established in the authorization and the therapeutic protocol of the centre.	Prescriber has to justify need in the clinical history; Informed consent is required; Prescriber must notify adverse events; Prescriber must comply with established recommendations and therapeutic protocols.
Switzerland Federal law on medicinal products and medical devices, Art 9, Art 26	If it is proven that there is no authorized or available alternative medicine that is applicable and equivalent.	
Hungary Art 25 of Act XCV (2005), subsection 6	(1) If treatment with licensed medicine is not possible or unsuccessful Or (2) Access to licensed medicine is inhibited to an extent that would likely delay treatment.	Prescriber must ensure that (1) Based on experimental evidence, medicine offers potential of successful treatment or improve/stabilize patient condition; Medicine is licensed for distribution in Hungary or another country; Prescriber is specialist in specific therapeutic

		area; Prescriber's request for use of this medicine in specific patient has been granted by government body for pharmaceuticals.' (2) Risk/benefit balance of off-label medicine is better than that of the licensed medicine; Based on experimental evidence, medicine offers potential of successful treatment or improve/stabilize patient condition; The SmPC of licensed medicine does not contain contra-indication regarding requested unlicensed indication.

Table 2: National measures to regulate reimbursement of off-label medicines[a]

Country	When off-label prescribing?	How?
Belgium	There is a Special Solidarity Fund for individual patients, but the fund has limited resources. This is because the Belgian reimbursement regulation is based on a positive list of reimbursed products. Consequently, off label can potentially qualify for reimbursement, nor necessary linked to an indication or age category.	
Hungary		Case-by-case evaluation: decision to reimburse is taken based upon circumstances (including existing alternatives and reasons why these are not sufficient) and costs.
Germany Section 92 para (1) Nr. 6 SGB V		The German Agency decides if off-label medicines are reimbursed based on a scientific evaluation by its off-label expert commissions. Costs should be refunded also if there are only weak references for efficacy, on condition that the patient suffers from a life-threatening condition and alternatives are missing.
Greece Official Gazette 545/B'/01-03-2012 Law 4316/2014		Ministerial decree is required in special cases and according to international bibliographic references. Off-label indications could be reimbursed if included in therapeutic protocols approved by the Central Committee of Health Council.

Table 3: National guidance to professionals on off-label medicine use in children[a]

Country	When off-label prescribing?	How?
Belgium		When a suitable tested and approved alternative is available, prescribing physicians' liability may be at (increased) risk if safety issues arise. If an adverse event arises through the use of that drug, the treating physician would have the burden of proof to demonstrate that its use was performed as standard of care. Key characteristics: usual or common practice, scientific basis and informed consent.
Lithuania Law of Pharmacy No. X-709 (2006) Law of Patients' rights, safety and compensation of harm No. I-1562 (1996)		Off-label use of licensed medicines is possible based on the decision of a council or group of clinical pharmacologists if applicable. In the outpatient setting it is possible to prescribe off-label and extemporaneous medicines based on experience and personal decision.
Sweden SFS 2010:659 and SFS 2014:821		If there is sufficient scientific evidence and clinical experience to prescribe medicine Informed consent is required.
United Kingdom Good practice in prescribing and managing medicines and devices, 2013		Prescriber must be convinced there is sufficient evidence or experience of using medicine to demonstrate its safety and efficacy; NICE publishes evidence summaries for off-label and unlicensed medicines. Prescriber has responsibility for prescribing the medicine; Prescriber is responsible for overseeing patient's care, monitoring and follow-up (or should ensure this is done by another suitable physician); Prescriber must have clear, accurate and legible record of prescribed medicines and reasons for prescribing medicine off-label; Informed consent is required. **Paediatric:** **Royal College of Paediatrics and Child Health (Rev 2, 2013) [24]:** Where available, an appropriate licensed preparation should be prescribed and supplied in preference to an unlicensed preparation. In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain consent of parents, caregivers and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications (off-label)[b].

The Netherlands Art 68 of Medicines Act	If relevant professional body has developed protocols or professional standards with regard to the specific off-label use. If protocols or standards are under development, prescriber and pharmacist are required to consult each other.	**<u>Paediatric:</u>** **Dutch Paediatric Society (Rev 4, 2018) [26]:** The Dutch Paediatric Society has accepted the National Paediatric Formulary as expert guideline. Off-label use is considered appropriate if there is a medical need (no registered medicine available or registered medicine is suboptimal for individual patient]. There should be a positive balance between expected efficacy and risks based on available literature and assessed within multidisciplinary setting. Informed consent is required unless off-label use is documented in National Paediatric Formulary or in professional guideline. The prescribing physician should inform parents/caregivers/child about the benefits and risks of off-label or unlicensed use of medicines. Off-label treatment with medicines should be regularly and rigorously monitored and adverse events should be reported nationally.

Tables 1-3: [a]Based on information provided by EAP members and data included in [4,27,30]; [b]Used definitions for off-label and unlicensed use may vary across countries and publications[2]. For example, in the UK, off-label use of drugs is referred to as "unlicensed use of licensed drugs". No data: countries not participating in EU study: e.g., Luxemburg, Norway, Switzerland, Iceland, Latvia, Poland, Romania, Croatia, Albania, Macedonia, Serbia, Bosnia and Herzegovina.